Neonatal hypertyrosinemia and evidence for deficiency of ascorbic acid in Arctic and subarctic peoples

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Summary: Hypertyrosinemia (tyrosine concentration in whole blood > 0.42 mmol/l or 7.5 mg/dl is prevalent among Inuit newborn of the Canadian Eastern Arctic. The rate was 14.8 per 100 newborn between January 1970 and December 1972 (first survey period) and 6.2/100 between January 1973 and September 1974 (second survey period); the corresponding rates among Indian newborn of Nouveau Québec were 2.6 and 2.2%. Among Anglo-Saxons the rate was less than 0.5% and in French Canada it commonly exceeded 0.94%.

Serum concentrations of ascorbic acid were low (⩽ 0.25 mg/dl) in the pregnant and age-matched adult Inuit when measured by Nutrition Canada during the first survey period. The percentages of Inuit children (up to 4 years old) and pregnant women at "high risk" for scurvy (serum concentration of ascorbic acid < 0.2 mg/dl) were 14.8 and 47.1, respectively; the corresponding national percentages were 3.0 and 2.2, respectively.

Deficiency of ascorbic acid in pregnant women is probably the cause of the unusual prevalence of neonatal hypertyrosinemia among the native Arctic and subarctic peoples because ascorbic acid is required to maintain optimal activity of *p*-hydroxyphenylpyruvic acid hydroxylase and to permit normal oxidation of tyrosine.

Résumé: *Hypertyrosinémie néonatale et évidence de déficience d'acide ascorbique chez les peuples arctiques et subarctiques*

L'hypertyrosinémie (concentration de tyrosine dans le sang total, supérieure à 0.42 mmol/l ou 7.5 mg/dl) est prédominante parmi les nouveau-nés Inuits de l'Arctique Canadien de l'est. Le taux était de 14.8 par 100 nouveau-nés de janvier 1970 à décembre 1972 (première période d'étude) et de 6.2/100 entre janvier 1973 et septembre 1974 (seconde période d'étude). Les taux correspondants chez les nouveau-nés Indiens du Nouveau Québec étaient de 2.6 et 2.2% pour ces deux périodes. Parmi les Anglo-Saxons le taux était inférieur à 0.5% et au Canada français il dépassait souvent 0.94%.

Les concentrations sériques d'acide ascorbique, mesurées par "Nutrition Canada" durant la première enquête, étaient faibles (⩽ 0.25 mg/dl) chez les femmes enceintes et les adultes Inuits d'âge correspondant. Les pourcentages d'enfants Inuits (jusqu'à l'âge de 4 ans) et des femmes enceintes qui étaient au "risque élevé" pour le scorbut (concentration sérique d'acide ascorbique, < 0.2 mg/dl) étaient de 14.8 et 47.1, respectivement; les pourcentages correspondants de la population nationale étaient de 3.0 et 2.2, respectivement.

La déficience d'acide ascorbique chez les femmes enceintes est probablement la cause de la prédominance d'hypertyrosinémie néonatale chez les peuples indigènes de l'Arctique et des régions subarctiques: l'acide ascorbique est en effet nécessaire pour maintenir une activité optimale de l'hydroxylase de l'acide *p*-hydroxyphénylpyruvique et pour permettre une oxydation normale de la tyrosine.

Man depends on an environmental source of ascorbic acid for his endogenous needs[1] because of an isogenic mutation causing a deficiency of the enzyme that converts the precursor hexonic acid, L-gulonolactone, to L-ascorbic acid. The amount of ascorbic acid in tissues is determined by the balance between dietary intake and metabolic turnover. The latter is influenced by loss through oxidation to dehydroascorbic acid and conversion to oxalic acid, and also by reclamation from urine by a mediated transport process in the renal tubule. Although as little as 10 mg/d of ascorbic acid prevents scurvy in man, a higher daily intake, approximately 0.5 mg/kg body weight, is recommended as a daily allowance for healthy adults.[1]

Ascorbic acid is required for optimal activity of several enzyme-dependent reactions, one of which is oxidation of the tyrosine derivative *p*-hydroxyphenylpyruvic acid (*p*-HPPA) to homogentisic acid.[2,3] This complex reaction is catalyzed by the copper-containing hydroxylase *p*-hydroxyphenylpyruvate ascorbate:oxygen oxidoreductase hydro-

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xylating (EC [enzyme classification] 1.14.2.2). Depletion of tissue ascorbic acid impairs the activity of *p*-HPPA hydroxylase and thus impairs the oxidation of tyrosine.

It has long been known that inadequate ascorbate nutrition in the newborn infant results in transient tyrosyluria and hypertyrosinemia,[4] which respond to administration of ascorbic acid.[5] The condition can be largely prevented by supplementing the diet with 100 mg of ascorbic acid per day in the immediate postnatal period.[6]

Discovery of an unusually high prevalence of neonatal hypertyrosinemia among native infants born in the eastern Arctic and subarctic led us to study ascorbic acid nutrition in those regions.

Screening program

During the past 4 years a service-oriented screening program has been available for measuring the tyrosine concentration in whole blood of all infants born in settlements in the eastern Arctic and subarctic (Baffin Zone, NWT). Capillary blood is collected on filter paper (Schleicher and Schuell, no. 903) from the heel of the infant at the time of discharge from the nursery and is analysed by an automated fluorimetric method for tyrosine[7] at the central blood-screening laboratory of the Quebec Network of Genetic Medicine (QNGM). Additional tests for up to 50 acquired and inherited metabolic disorders are also provided in the program.[8,9] One of the regional genetics centres in the QNGM is at the Montreal Children's Hospital; this institution also participates in a health-care program for Baffin Zone sponsored by the federal Department of Northern Affairs.

Definition

Hypertyrosinemia is defined by the QNGM as a concentration of tyrosine in whole blood in excess of 0.42 mmol/*l* (7.5 mg/dl). This value is more than three standard deviations above the mean for the newborn population served by the screening network. It was selected after analysis of the "costs", in specificity and sensitivity, when screening simultaneously for neonatal hypertyrosinemia and hereditary tyrosinemia, a potentially fatal genetic disease, which occurs at an increased frequency in a sector of the Québec population.[2,10] This definition of hypertyrosinemia does not differ appreciably from that used in our earlier studies of neonatal hypertyrosinemia and its prevalence among the newborn.[5,11]

Table I—Prevalence of neonatal hypertyrosinemia observed by Québec Network of Genetic Medicine

Population	No. of samples tested	Prevalence of hypertyrosinemia* (per 100 newborn)	
Québec	126 000	0.94	
Gaspé region			0.90
Trois-Rivières région			1.40
Montréal region (Anglo-Saxon)†			0.41
Nouveau Québec‡			
First survey§	345	2.6	
Second survey¶	311	2.2	
Eastern Arctic#			
First survey§	162	14.8	
Second survey¶	196	6.2	

*Concentration of tyrosine in whole blood: > 0.42 mmol/*l*.
†Infants usually fed proprietary formulas containing vitamin C and screened previously; prevalence data correspond to those reported for other Anglo-Saxon populations.[11]
‡Area bounded to the south by the Eastmain River, Lake Nichicun and Labrador City, to the east by Labrador, to the north by Ungava Bay and Hudson Strait, and to the west by James Bay and Hudson Bay. Indian population surveyed.
§Jan. 1, 1970 to Dec. 31, 1972
¶Jan. 1, 1973 to Sept. 30, 1974
#Inuit population.

Survey methods

Our Arctic survey covered two periods: Jan. 1, 1970 (when screening for disorders of amino acids began) to Dec. 31, 1972 (when the Nutrition Canada survey ended; it had begun in September 1970) and Jan. 1, 1973 to Sept. 30, 1974 (the time the report was initiated).

Under the auspices of the nutrition committee of the Canadian Paediatric Society and Dr. Allen L. Forbes, former director of the nutrition bureau of Health and Welfare Canada, we were also given access to then unpublished data from the Nutrition Canada national survey pertaining to ascorbic acid nutrition in the Inuit and Indian populations and in the non-native populations in the Québec and national samples.[12,13]

Serum concentrations of ascorbic acid were measured by Nutrition Canada in the populations covered by our first survey; the corresponding dietary intakes were assessed at personal interviews by the 24-hour dietary recall method.

Results

The prevalence of neonatal hypertyrosinemia was high among Inuit and Indian newborn infants in the eastern Arctic and subarctic in both survey periods compared with newborn populations to the south in urban and rural Québec (Table I). Among infants in French Canada it was about twice the expected rate — 0.94%, compared with about 0.5%[11] — and changed very little between the two survey periods.

From the results of the combined investigation of ascorbic acid nutrition and blood tyrosine concentration (Table II) the following can be observed:

1. As ascorbic acid intake increases from less than 30 to more than 100 mg/d in the subjects in this study, serum concentration of ascorbate increases from less than 0.2 to more than 0.6 mg/dl.
2. The median serum concentration for ascorbic acid is low (≤ 0.25 mg/dl) in the pregnant Inuit and also in the nonpregnant female and male Inuit control subjects.
3. Among children in the first survey 14.3% of the

Table II—Ascorbic acid: dietary intake and serum concentration reported by Nutrition Canada*

Population, age (yr) and sex	Median intake (mg/d)	Median serum concentration (mg/dl)	% of group at risk†
Eskimo			
0-4	39	0.66	*14.3*
20-39			
Male	30	0.14	*57.4*
Female	26	0.17	*53.4*
Pregnant	28	0.25	*47.1*
Indian			
0-4	65	1.00	3.1
20-39			
Male	48	0.39	13.6
Female	46	0.48	13.2
Pregnant	62	0.70	*10.3*
Québec			
0-4	80	0.89	3.3
20-39			
Male	92	0.62	12.9
Female	74	0.66	12.2
Pregnant	130	0.97	3.6
All Canada			
0-4	81	1.20	3.0
20-39			
Male	94	0.78	6.8
Female	70	0.78	6.5
Pregnant	133	1.01	3.2

*From data of 1970-72 survey, published in individual reports for the provinces for all Canada[12] and for Indians and Eskimos.[13]
†High risk (for scurvy): serum concentration of ascorbic acid < 0.2 mg/dl; values clearly discordant with national trend are italicized.

Inuit were at high risk for scurvy (serum concentration of ascorbate < 0.2 mg/dl), whereas the national figure was only 3%. Among pregnant Inuit and age-matched controls about 50% were at high risk for scurvy, whereas the national figure was less than 7%.[12,13]

4. The lowest median serum concentration of ascorbic acid among pregnant women in the nationwide survey was in the Inuit (0.25 mg/dl), to whom are born the infants with the highest known prevalence of neonatal hypertyrosinemia in Canada (Table I).

Discussion

There are several potential pitfalls in deducing that neonatal hypertyrosinemia today in the Arctic is the direct result of a deficiency of ascorbic acid in pregnant women. First, Nutrition Canada surveyed Inuit of four widely dispersed Arctic settlements that included only 18 pregnant woman and only 33 children (up to 4 years old), of whom probably no more than 6 were young infants. Moreover, there is no guarantee that it is this population of Inuit who were screened for tyrosinemia. Whereas the present data suggest hypoascorbicacidemia is prevalent in Northern peoples, and hence tyrosine metabolism in their offspring is defective, serial observations on mother–newborn pairs are required to confirm this impression.

A second point of concern is the validity of the ascorbic acid analysis in the serum samples shipped from the Arctic to the central laboratory in Ottawa that served the Nutrition Canada survey. Because ascorbic acid is lost from serum in storage,[14,15] precautions were taken to retard the oxidation of ascorbic acid in serum samples.[12,14] We have been assured that the delays in analysing the Arctic samples were not appreciably different from those for all other samples processed in the national survey. Therefore, the relative differences in the ascorbic acid content of Inuit and Québec samples appear to be real, but further observations on paired maternal–infant samples processed in identical fashion in the various populations are necessary.

Third, the subjective data on estimates of ascorbic acid intake are the least reliable in the present study. None the less, the data suggest that Arctic Inuit adults consume little ascorbic acid. Indians in the North are more like southern Canadians in their serum concentrations of ascorbic acid, a feature apparently determined by their ascorbate intake, which is higher than that of the Inuit. The likelihood that the dietary intake data truly correlate with the serum concentration finds support in the Nutrition Canada descriptions of "diffuse bleeding gums": the prevalence is highest in the pregnant women with the lowest serum concentrations of ascorbic acid, namely, the Inuit, among whom it is 2.2 times the national rate.

Our particular concern about ascorbic acid nutrition in Northern peoples stems from the discovery of a high prevalence of neonatal hypertyrosinemia in the Inuit newborn and, to a lesser extent, in the Indian newborn (Table I). Screening for tyrosinemia, as performed in this study, is not affected by artefacts of sample-handling over distance or time. Three interrelated factors contribute to the production of hypertyrosinemia in the newborn.[2,3,5,16] First, there is a diminished amount of the *p*-HPPA hydroxylase apoenzyme in the mammal in the perinatal period; second, the enzyme is readily inhibited (oxidized) by its substrate, so it is more easily inhibited when tyrosine intake is high and apoenzyme concentrations are low; third, ascorbic acid is required to prevent apoenzyme inhibition, and the relatively low concentrations of ascorbic acid in human or cow's milk can do little to repair ascorbate nutrition if it is impoverished in the newborn. The Inuit newborn who is not unduly premature, and therefore not particularly vulnerable to hypertyrosinemia,[2,5] is now more commonly fed by bottle than at the breast and therefore ingests relatively more tyrosine. And if he has been deprived of ascorbic acid during intrauterine development because of culturally induced changes in maternal nutrition hypertyrosinemia will develop. This simple mechanism explains the current high prevalence of neonatal hypertyrosinemia in the Inuit newborn. The same phenomenon may, to a lesser extent, be occurring in the Indians, thus accounting for the high prevalence of neonatal hypertyrosinemia in that population.

The decrease in the prevalence of neonatal hypertyrosinemia in the Arctic between the first survey and the second suggests that a change in infant feeding (related to protein or ascorbic acid) has taken place recently. We have not been able to determine, in any but anecdotal fashion, that this is the case because of the difficulties in obtaining data from appropriate authorities.

Although neonatal hypertyrosinemia is generally believed to be a benign transient condition, affecting only about 0.5% of all Caucasian newborns,[2,11] there is still lingering concern that it is not completely free of harm,[17-21] particularly if persistent and associated with low birth-weight; indeed, impaired postnatal mental and motor development have been reported in association with persistent neonatal hypertyrosinemia.[17-21] As a result, we believe it is important to pursue the interpretation of this unexpectedly prevalent condition in our Arctic and subarctic peoples. In the continuing investigation we hope also to determine why neonatal hypertyrosinemia is twice as common in the French Canada population as in other southern Canadians.

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